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Corticosteroids for parasitic eosinophilic meningitis (Review)

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[Intervention Review]

Corticosteroids for parasitic eosinophilic meningitis

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ABSTRACT

Background

Angiostrongylus cantonensis (*A. cantonensis*) is the major cause of infectious eosinophilic meningitis. Dead larvae of this parasite cause inflammation and exacerbate symptoms of meningitis. Corticosteroids are drugs used to reduce the inflammation caused by this parasite.

Objectives

To assess the efficacy and safety of corticosteroids for the treatment of eosinophilic meningitis.

Search methods

We searched CENTRAL (2014, Issue 11), MEDLINE (1950 to November Week 3, 2014), EMBASE (1974 to December 2014), Scopus (1960 to December 2014), Web of Science (1955 to December 2014), LILACS (1982 to December 2014) and CINAHL (1981 to December 2014).

Selection criteria

Randomised controlled trials (RCTs) of corticosteroids versus placebo for eosinophilic meningitis.

Data collection and analysis

Two review authors (SiT, SaT) independently collected and extracted study data. We graded the methodological quality of the RCTs. We identified and analysed outcomes and adverse effects.

Main results

We did not identifiy any new trials for inclusion or exclusion in this 2014 update. One study involving 110 participants (55 participants in each group) met our inclusion criteria. The corticosteroid (prednisolone) showed a benefit in shortening the median time to resolution of headaches (five days in the treatment group versus 13 days in the control group, P value < 0.0001). Corticosteroids were also associated with smaller numbers of participants who still had headaches after a two-week course of treatment (9.1% versus 45.5%, P value < 0.0001). The number of patients who needed repeat lumbar puncture was also smaller in the treatment group (12.7% versus 40%, P value = 0.002). There was a reduction in the median time of analgesic use in participants receiving corticosteroids (10.5 versus 25.0, P value = 0.038). There were no reported adverse effects from prednisolone in the treatment group.

Authors' conclusions

Corticosteroids significantly help relieve headache in patients with eosinophilic meningitis, who have a pain score of four or more on a visual analogue scale. However, there is only one RCT supporting this benefit and this trial did not clearly mention allocation concealment and stratification. Therefore, we agreed to grade our included study as a moderate quality trial. Future well-designed RCTs are necessary.

PLAIN LANGUAGE SUMMARY

Corticosteroids for the treatment of parasitic eosinophilic meningitis

Review question

Do corticosteroids reduce inflammation in the membrane of the brain caused by parasites?

Background

Eosinophilic meningitis is an inflammation of the membrane covering the brain, the causes of which can be broadly categorised into infectious and non-infectious. Among the infectious aetiologies, *Angiostrongylus cantonensis*, a rat lung worm, is the major cause of eosinophilic meningitis. It occurs principally in South-East Asia and throughout the Pacific basin. However, this parasite has spread beyond the Pacific basin and is now found in regions of North America due to infected ship rats. Severe headache, which is self limiting, is the main complaint. The headache is probably due to an immune response to the dead parasites. Other signs and symptoms include neck stiffness and pain, visual disturbances, nausea, vomiting, paraesthesia and hyperaesthesia. Corticosteroids are drugs that reduce inflammation, which can occur in eosinophilic meningitis due to dead larvae.

Study characteristics

We conducted a systematic review and meta-analysis of randomised controlled trials of corticosteroids for treating eosinophilic meningitis. The evidence is current to December 2014. We found only one randomised controlled trial that matched our criteria. This trial included 129 patients (63 in the treatment group, prednisolone 60 mg/day, divided into three doses for two weeks and 66 in the control group, placebo). However,19 patients were lost to follow-up.

Key results

The included study showed that the median time to resolution of headaches was lower in the group treated with prednisolone (10.5 days versus 25 days) and the number of patients who still had headaches after 14 days was lower in the prednisolone group compared to the control (9.1% versus 45.5%). There were statistically significant differences, which favoured the treatment group, in other outcomes including the frequency of acetaminophen (paracetamol) use (median of number of times used) amongst those who still had headaches after 14 days of prednisolone treatment and the mean time until complete disappearance of headache. The number of patients who needed repeat lumbar puncture was also smaller in the treatment group. There were no reported adverse effects from prednisolone in the treatment group. Corticosteroids significantly help relieve headache in patients with eosinophilic meningitis, who have a pain score of four or more on a visual analogue scale.

Quality of the evidence

Given the lack of allocation concealment and blinding (especially in a trial with subjective outcomes), and the attrition (loss of participants), we graded our evidence as moderate quality.

BACKGROUND

Description of the condition

Eosinophilic meningitis is defined by the presence of greater than or equal to 10 eosinophils per microlitre of cerebrospinal fluid (CSF), or greater than or equal to 10% of the total CSF leukocyte count (Kuberski 1981). The causes of eosinophilic meningitis can be broadly categorised as infectious and non-infectious. Where the cause is non-infectious, the aetiologies are leukaemia or lymphoma with central nervous system (CNS) involvement (Hodgkin's), idiopathic hypereosinophilic syndrome (Moore 1985), allergic reactions of the meninges to ventriculoperitoneal shunt (Kennedy 1988; Tung 1991), medications such as non-steroidal anti-inflammatory drugs (NSAIDs), ciprofloxacin, trimethoprim-sulfamethoxazole (Asperilla 1989; Patey 1998; Quinn 1984), and intraventricular vancomycin or gentamicin (Grabb 1992). Intravenous drug injections among drug users have also been shown to cause sterile eosinophilic meningitis and arachnoiditis (Rossetti 2002). When the cause is infectious, the pathogens can be parasites, viruses, bacteria or fungi, with parasites being the most common pathogens. The three predominant agents are *Angiostrongylus cantonensis* (*A. cantonensis*), *Gnathostoma spinigerum* (*G. spinigerum*) and *Baylisascaris procyonis* (*B. procyonis*). Among these, *A. cantonensis*, the rat lung worm, is the principal aetiologic agent of human eosinophilic meningitis.

In *A. cantonensis*, humans are infected accidentally by ingesting raw infected molluscs, vegetables contaminated with mollusc slime and carrier hosts such as freshwater prawns, crabs, frogs and planaria (Tsai 2004). This parasite has spread progressively throughout the Pacific basin and is now found in regions of the United States due to intercontinental dissemination of infected ship rats (Campbell 1988; Kliks 1992). The penetration of this host-parasite system into the tropical and subtropical areas of Africa, the Indian subcontinent, the Caribbean and the temperate Gulf Coast region of the United States is of considerable public health importance.

Eosinophilic meningitis occurs principally in South-East Asia and throughout the Pacific basin. People in these areas or travellers who eat local uncooked food are at risk of contracting this disease. According to studies in Thailand, there are approximately 1000 new cases every year, most of them among the working-aged population. The incubation period ranges from six to 31 days following ingestion. Severe headache is the main complaint. Although the headache is self limiting, it is a distressing symptom for the patient. Other signs and symptoms include neck stiffness and pain, visual disturbances, nausea, vomiting, paraesthesia ('pins and needles') and hyperaesthesia (Slom 2003; Tsai 2004). Other signs and symptoms are also self limiting; paraesthesia can persist for weeks but does resolve with time. Paralysis of the facial and extraocular muscles has been reported but generally resolves spontaneously (Kuberski 1979; Podwall 2004).

Description of the intervention

Eosinophilic meningitis is primarily treated supportively with analgesics, sedatives and lumbar punctures to relieve high CSF pressure. These interventions can lead to dramatic clinical improvements. The natural steroid cortisol, a main glucocorticoid, is secreted by the adrenal cortex. Synthetic steroids include prednisolone, methylprednisolone, betamethasone, dexamethasone and triamcinolone hydrocortisone. Steroids can be administered orally, intravenously or by inhalation therapy. Some reports claim a benefit with steroids for eosinophilic meningitis (Koo 1988; Reid 1984), whereas some studies in Thailand have shown no such benefits (Chotmongkol 2002; Punyagupta 1975). Recently, a randomised, placebo-controlled trial conducted in Thailand demonstrated the effectiveness and safety of steroids for eosinophilic meningitis (Chotmongkol 2004).

Antihelminthics are a class of antiparasitic drugs. Since the main parasites for eosinophilic meningitis are roundworms or nematodes, the antiparasitics used are antinematodes, such as mebendazole, albendazole and thiabendazole. Specific antihelminthic treatment alone is controversial. A study has shown the benefits of combining albendazole and corticosteroids (Chotmongkol 2000). However, the outcome is similar to treatment with corticosteroids alone (Chotmongkol 2009).

How the intervention might work

Steroids act by inducing an anti-inflammatory response in the body. They are used to treat inflammatory diseases such as arthritis, colitis, dermatitis and bacterial meningitis. Dead larvae cause an inflammatory reaction and exacerbate symptoms, therefore steroids can be used to regulate this natural response. However, the use of steroids can cause adverse effects such as skin lesions, weight gain, Cushing's syndrome, cataracts, osteoporosis, hyperglycaemia, gastrointestinal bleeding, slow healing and psychosis immune suppression. Most of these adverse effects are dose- and duration-dependent.

Why it is important to do this review

The benefit of steroids in the treatment of eosinophilic meningitis remains unclear, although they are sometimes used in clinical practice. This review aims to resolve this question.

OBJECTIVES

To assess the efficacy and safety of corticosteroids for the treatment of eosinophilic meningitis.

METHODS

Criteria for considering studies for this review

Types of studies

Randomised controlled trials (RCTs) of corticosteroids for eosinophilic meningitis.

Types of participants

Participants aged 15 years or older, of any sex, with eosinophilic meningitis. The diagnosis of eosinophilic meningitis is usually made from a medical history, dietary history, clinical signs and symptoms, and cerebrospinal fluid (CSF) analysis. Imaging of the brain is sometimes used to exclude other potential causes. We excluded participants if they were already taking steroids at the time of the study.

Types of interventions

Steroids (any type and dosage) versus placebo.

Types of outcome measures

Primary outcomes

1. Resolution rates (complete disappearance of headache within two to four weeks after completion of the treatment).

Secondary outcomes

1. Percentage of analgesics used to relieve symptoms.
2. Percentage of therapeutic lumbar punctures used to relieve headaches.
3. Time to complete resolution of headache after treatment.
4. Adverse effects of medication.

Search methods for identification of studies

Electronic searches

For this 2014 update of we searched the Cochrane Central Register of Controlled Trials (CENTRAL 2014, Issue 11) (accessed 10 December 2014), which contains the Cochrane Acute Respiratory Infections (ARI) Group's Specialised Register, MEDLINE (May 2012 to November week 3, 2014), EMBASE (June 2012 to December 2014), Scopus (2012 to December 2014), Web of Science (2012 to December 2014), LILACS (2012 to December 2014) and CINAHL (May 2012 to December 2014).

Previously we searched CENTRAL (2012, Issue 6), MEDLINE (1950 to July Week 4, 2012), EMBASE (1974 to July 2012), Scopus (1960 to July 2012), Web of Science (1955 to July 2012), LILACS (1982 to July 2012) and CINAHL (1981 to July 2012).

We used the search strategy in Appendix 1 to search MEDLINE and CENTRAL. We combined the MEDLINE search with the Cochrane Highly Sensitive Search Strategy for identifying randomised trials in MEDLINE: sensitivity-maximising version (2008 revision); Ovid format (Lefebvre 2011). We adapted the search strategy to search EMBASE (Appendix 2), Scopus (Appendix 3), Web of Science (Appendix 4), LILACS (Appendix 5) and CINAHL (Appendix 6). We imposed no language or publication restrictions.

Searching other resources

We searched the trials registries World Health Organization (WHO) International Clinical Trials Registry Platform (ICTRP) and ClinicalTrials.gov (latest search 29 July 2014) for completed and ongoing trials. We identified other relevant trials by searching the reference lists of included trials and handsearching conference abstracts and non-indexed articles.

Data collection and analysis

Selection of studies

Two review authors (SiT, SaT) independently selected studies from the search results. We obtained the full text of the article in case we were in doubt about the trial's eligibility. We resolved any disagreement between the review authors by discussion.

Data extraction and management

Two review authors (SiT, SaT) independently extracted data from the studies using a predefined protocol. We resolved any disagreement between the review authors by discussion. Two review authors (SiT, SaT) independently collected data from the potential studies. One review author (CN) entered the information from the data extraction forms and analysed the quantitative data using Review Manager software (RevMan 2014).

Assessment of risk of bias in included studies

We assessed risk of bias in the included studies across six domains (sequence generation, allocation concealment, blinding of participants, blinding of personnel, blinding of outcome assessors, incomplete outcome data, selective outcome reporting, and other potential sources of bias). Two review authors (SiT, SaT) judged each domain as low risk of bias, high risk of bias, or unclear risk of bias, based on the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011). In case of disagreement, the third review author (CN) acted as arbitrator.

Measures of treatment effect

We measured the treatment effect of the studies using the risk ratio (RR) with 95% confidence intervals (CIs) for dichotomous outcomes (percentage of patients who still had a headache after two weeks completion of treatment, analgesics used to relieve symptoms, therapeutic lumbar puncture to relieve headache and adverse effects of medications).

We used the mean difference (MD) or standardised mean difference (SMD) with 95% CIs for continuous outcomes (time to complete disappearance of headache after treatment).

Unit of analysis issues

The unit of analysis was the individual participant.

Dealing with missing data

We contacted the authors of the included studies by email to request missing data. In case of missing participants due to drop-out, we used an intention-to-treat (ITT) analysis.

Assessment of heterogeneity

We did not investigate the heterogeneity of treatment effect between studies as there was only one study that met our inclusion criteria.

Assessment of reporting biases

We did not assess reporting bias.

Data synthesis

As there was only one included study, we were unable to pool the treatment effects.

Subgroup analysis and investigation of heterogeneity

We did not conduct a subgroup analysis to investigate the source of heterogeneity.

Sensitivity analysis

We did not carry out sensitivity analysis.

RESULTS

Description of studies

See: Characteristics of included studies and Characteristics of excluded studies tables.

Results of the search

We retrieved 21 records from this 2014 update search but we did not identify any new trials for inclusion or exclusion. Previously we retrieved 90 records from our search of the electronic resources. We found one eligible trial (Chotmongkol 2000). We also identified one trial that was close to meeting our inclusion criteria but the study compared the treatment effects of prednisolone (corticosteroid) plus albendazole (antihelminthic) with prednisolone alone, not with placebo (Chotmongkol 2009).

Included studies

Only one study was eligible for inclusion (Chotmongkol 2000). In this study, the participants were patients aged 15 years or older with a diagnosis of eosinophilic meningitis based on cerebrospinal fluid (CSF) findings of ≥ 10% eosinophils. One hundred and twenty-nine participants (63 in the treatment group and 66 in the control group) were enrolled. However, 19 participants (eight in the treatment group and 11 in the control group) were lost to follow-up and data were incomplete.

The participants, who were stratified according to the severity of headache and CSF opening pressure, were randomised to receive either treatment or placebo. The intervention consisted of prednisolone 60 mg/day divided into three doses for two weeks. During the treatment, patients were given two tablets of acetaminophen (500 mg tablet) every four to six hours to relieve headache; repeat therapeutic lumbar punctures were conducted if the headache was not resolved using acetaminophen.

The trial authors recorded the frequency of acetaminophen use and the percentage of patients who needed lumbar punctures. Both groups also took alum milk orally, divided into three doses after meals. Participants were evaluated every day for two weeks, then every two weeks until they completely recovered. The severity of headaches was assessed using a visual analogue scale. The short-term adverse effects, such as gastrointestinal bleeding and hyperglycaemia, were assessed. There were no disagreements on the inclusion or exclusion of studies between the review authors extracting study data. We did not need to contact any trial authors to provide additional information for this version of the review.

Excluded studies

We excluded five studies that did not fit our inclusion criteria. Four studies were not RCTs (Chotmongkol 2004; Chotmongkol 2006; Chotmongkol 2009; Sawanyawisuth 2004); and one study compared prednisolone plus albendazole with prednisolone alone, not with placebo (Chotmongkol 2009).

Risk of bias in included studies

The overall risk of bias is presented graphically in Figure 1 and summarised in Figure 2.

Figure 1. 'Risk of bias' graph: review authors' judgements about each risk of bias item presented as percentages across all included studies.

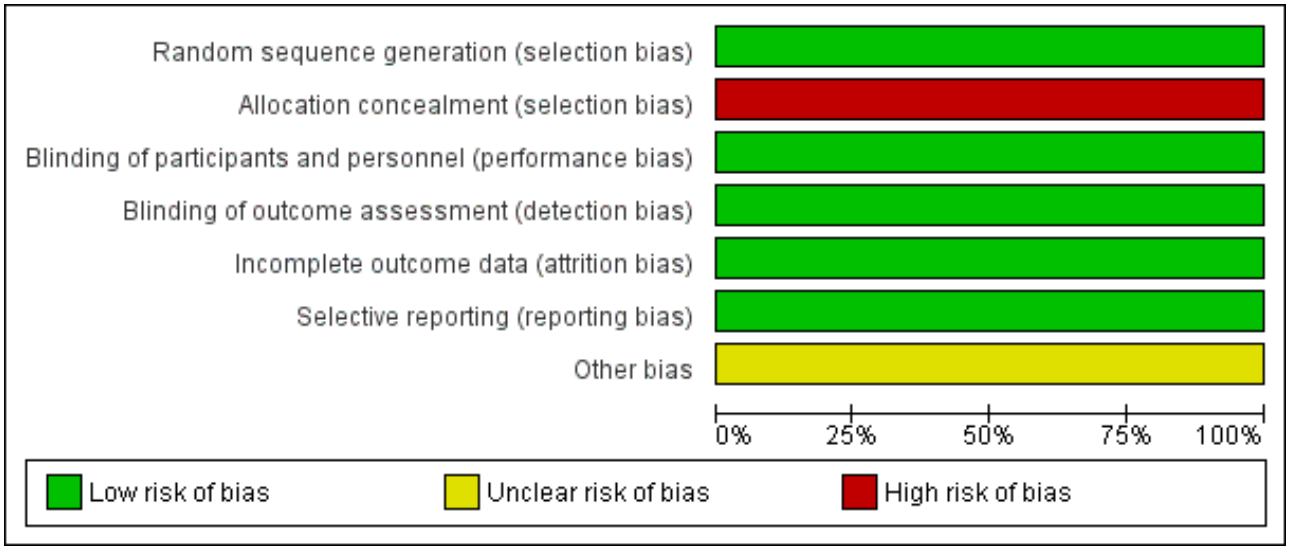
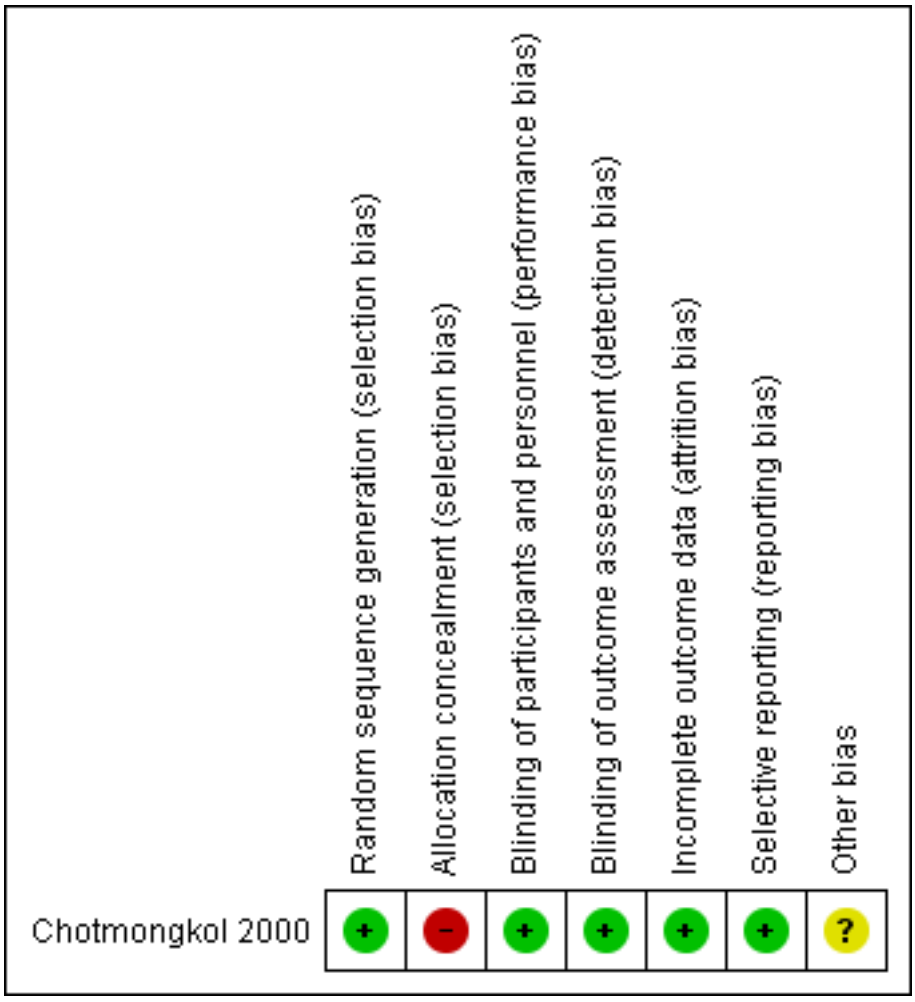


Figure 2. 'Risk of bias' summary: review authors' judgements about each risk of bias item for each included study.



Allocation

In our included study, the sequence generation used a block-of-four randomisation and was therefore adequate (Chotmongkol 2000). However, allocation concealment was not mentioned in this study, which can lead to selection bias (Schulz 2002).

Blinding

Chotmongkol 2000 used a placebo as a control and so the participants and investigators, including outcome assessors, were blinded.

Incomplete outcome data

Nineteen participants were lost to follow-up (eight in the treatment group and 11 in the control group); the reasons were not adequately described in the study. In the worst-case scenario, if the missing participants in the treatment group still had headaches after 14 days, the number of participants who still had headaches would be 13/63 (20%); and for the control group it would be 25/66 (37%).

Selective reporting

There was no selective reporting of outcomes in this study. The trial authors described important outcomes mentioned in the methods of the study.

Other potential sources of bias

The baseline characteristics were not significantly different between the two groups in the study. However, the assessment of drug compliance was not mentioned in the results.

Effects of interventions

Primary outcomes

1. Resolution rates (complete disappearance of headache within two to four weeks after completion of the treatment)

There was a statistically significant difference in the outcomes. The number of patients who still had headaches after 14 days of prednisolone treatment was significantly higher in the control group (25 out of 55 (45.5%) versus 5 out of 55 (9.1%), risk ratio (RR) 0.2, P value = 0.00004). The mean time until complete disappearance of headache was significantly shorter in the treatment group (5 days versus 13 days, P value < 0.001).

Secondary outcomes

1. Percentage of analgesics used to relieve symptoms

The frequency of acetaminophen use (median of number of times) was lower in the treatment group: 10.5 versus 25, P value = 0.038.

2. Percentage of therapeutic lumbar punctures used to relieve headaches

The number of patients who needed repeat lumbar puncture was smaller in the treatment group: 7 (12.7%) versus 22 (40%), RR 0.32, P value = 0.002.

3. Time to complete resolution of headache after treatment

The (median) time to complete resolution of headache after treatment was shorter in the treatment group: 5 (1 to 60) days versus 13 (1 to 56) days, P value < 0.0001.

4. Adverse effects of medication

There were no reported adverse effects from prednisolone in the treatment group.

DISCUSSION

Summary of main results

The use of corticosteroids (prednisolone 60 mg/day) showed a beneficial effect in parasitic eosinophilic meningitis. The single study we included showed that a two-week course of prednisolone 60 mg/day in three divided doses shortened the length of headaches caused by eosinophilic meningitis, reduced the frequency of analgesic use and reduced the number of patients who needed therapeutic lumbar puncture (Chotmongkol 2000). There were no adverse effects from steroids reported in either group.

Overall completeness and applicability of evidence

According to our review, based on one included study, a two-week course of prednisolone 60 mg/day in three divided doses was beneficial in adult patients aged ≥ 15 years who had eosinophilic meningitis, diagnosed by ≥ 10% eosinophils in the cerebrospinal fluid (CSF) (Chotmongkol 2000). All patients in the included study had a history of snail ingestion prior to the onset of eosinophilic meningitis. This study was conducted in Thailand, which is a low-income country; therefore, the role of corticosteroid use for eosinophilic meningitis in high-income countries is not clear. However, most eosinophilic meningitis occurs in low-income countries, since one of the risk factors is food hygiene.

For prednisolone use in relation to the severity of headache, we found that all patients in this study had at least a moderate degree of headache. Thus we assumed that prednisolone would be beneficial in treating moderate to severe headaches (4 to 7, moderate pain; 8 to 10, severe pain), but the role of corticosteroids in treating mild headaches needs to be addressed in future studies.

There were no adverse events reported in either group. No gastrointestinal bleeding or hyperglycaemia were reported in either group. The duration was not specified in the study but we could assume that there were no such adverse events for at least two weeks during the study period. Another study has compared the benefit of prednisolone alone versus prednisolone plus albendazole in the treatment of eosinophilic meningitis, but as this trial did not compare prednisolone plus albendazole versus placebo, we did not include this study in our review (Chotmongkol 2009). However, there were some points worth mentioning from this study. It did not show any advantages of prednisolone plus albendazole over prednisolone alone, leading to a conclusion that prednisolone plus albendazole was not superior to prednisolone alone in the treatment of eosinophilic meningitis.

Quality of the evidence

Given the lack of allocation concealment and blinding (especially in a trial with subjective outcomes), the attrition and the significant differences in outcomes, we agreed to grade our included study as a moderate quality trial (Chotmongkol 2000).

Potential biases in the review process

We did not identify any potential biases in the review process.

Agreements and disagreements with other studies or reviews

There have been no previous systematic reviews regarding the role of corticosteroids in eosinophilic meningitis. One prospective cohort study showed a benefit of a one-week course of 60 mg/day of prednisolone to relieve headaches caused by eosinophilic meningitis (Sawanyawisuth 2004). Another study conducted in Taiwan, which was a retrospective cohort study, showed that treatment with mebendazole (antihelminthic) plus dexamethasone (corticosteroid) shortens the duration of illness compared to those treated with analgesics alone, but the authors did not mention the dose of dexamethasone (Tsai 2001). In contrast, another study did not show any advantages of steroids in the treatment of eosinophilic meningitis (Punyagupta 1975). There were no adverse effects from corticosteroid use in the aforementioned studies.

AUTHORS' CONCLUSIONS

Implications for practice

To summarise, our analysis supports the use of corticosteroids in adults with acute eosinophilic meningitis with a pain score of four or more on a visual analogue scale. No consistency of benefit can be observed because we drew our findings from just one randomised controlled trial (RCT), which had limitations such as a lack of allocation concealment that may have led to an exaggeration of treatment benefit.

Implications for research

There has been only one RCT on this topic and the study lacked allocation concealment and blinding. Additional well-designed studies are needed to draw a firm conclusion on whether to treat acute eosinophilic meningitis with corticosteroids.

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REFERENCES

References to studies included in this review

Chotmongkol 2000 *{published data only}*

Chotmongkol V, Sawanyawisuth K, Thavornpitak Y. Corticosteroid treatment of eosinophilic meningitis. *Clinical Infectious Diseases* 2000;**31**(3):660-2.

References to studies excluded from this review

Chotmongkol 2004 *{published data only}*

Chotmongkol V, Wongjitrat C, Sawadpanit K, Sawanyawisuth K. Treatment of eosinophilic meningitis with a combination of albendazole and corticosteroid. *Southeast Asian Journal of Tropical Medicine and Public Health* 2004;**35**(1):172-4.

Chotmongkol 2006 *{published data only}*

Chotmongkol V, Wongjitrat C, Sawadpanit K, Sawanyawisuth K. Treatment of eosinophilic meningitis with a combination of albendazole and corticosteroid. *Southeast Asian Journal of Tropical Medicine and Public Health* 2006;**74**(6):1122-4.

Chotmongkol 2009 *{published data only}*

Chotmongkol V, Kittimongkolma S, Niwattayakul K, Intapan PM, Thavornpitak Y. Comparison of prednisolone plus albendazole with prednisolone alone for treatment of patients with eosinophilic meningitis. *American Journal of Tropical Medicine and Hygiene* 2009;**81**(3):443-5.

Sawanyawisuth 2004 *{published data only}*

Sawanyawisuth K, Limpawattana P, Bunsaracome P, Ninpaitoon B, Chotmongkol V. A 1-week course of corticosteroids in the treatment of eosinophilic meningitis. *American Journal of Medicine* 2004;**117**(10):802-3.

Additional references

Asperilla 1989

Asperilla MO, Smego RA Jr. Eosinophilic meningitis associated with ciprofloxacin. *American Journal of Medicine* 1989;**87**(5):589-90.

Campbell 1988

Campbell BG, Little MD. The finding of Angiostrongylus cantonensis in rats in New Orleans. *American Journal of Tropical Medicine and Hygiene* 1988;**38**(3):568-73.

Chotmongkol 2002

Chotmongkol V, Sawanyawisuth K. Clinical manifestations and outcome of patients with severe eosinophilic meningoencephalitis presumably caused by Angiostrongylus cantonensis. *Southeast Asian Journal of Tropical Medicine and Public Health* 2002;**33**(2):231-4.

Grabb 1992

Grabb PA, Albright AL. Intraventricular vancomycin-induced cerebrospinal fluid eosinophilia: report of two patients. *Neurosurgery* 1992;**30**(4):630-4.

Higgins 2011

Higgins JPT, Green S (editors). Cochrane Handbook for Systematic Reviews of Interventions Version 5.1.0 [updated March 2011]. The Cochrane Collaboration, 2011. Available from www.cochrane-handbook.org.

Kennedy 1988

Kennedy CR, Singer HS. Eosinophilia of the cerebrospinal fluid: late reaction to a silastic shunt. *Developmental Medicine and Child Neurology* 1988;**30**(3):386-90.

Kliks 1992

Kliks MM, Palumbo NE. Eosinophilic meningitis beyond the Pacific Basin: the global dispersal of a peridomestic zoonosis caused by Angiostrongylus cantonensis, the nematode lungworm of rats. *Social Science and Medicine* 1992;**34**(2):199-212.

Koo 1988

Koo J, Pien F, Kliks MM. Angiostrongylus (Parastrongylus) eosinophilic meningitis. *Reviews of Infectious Diseases* 1988;**10**(6):1152-62.

Kuberski 1979

Kuberski T, Wallace GD. Clinical manifestations of eosinophilic meningitis due to Angiostrongylus cantonensis. *Neurology* 1979;**29**(12):1566-70.

Kuberski 1981

Kuberski T. Eosinophils in cerebrospinal fluid: criteria for eosinophilic meningitis. *Hawaii Medical Journal* 1981;**40**(4):97-8.

Lefebvre 2011

Lefebvre C, Manheimer E, Glanville J. Chapter 6: Searching for studies. In: Higgins JPT, Green S (editors). Cochrane Handbook for Systematic Reviews of Interventions Version 5.1.0 [updated March 2011]. The Cochrane Collaboration, 2011. Available from www.cochrane-handbook.org.

Moore 1985

Moore PM, Harley JB, Fauci AS. Neurologic dysfunction in the idiopathic hypereosinophilic syndrome. *Annals of Internal Medicine* 1985;**102**(1):109-14.

Patey 1998

Patey O, Lacheheb A, Dellion S, Zanditenas D, Jungfer-Bouvier F, Lafaix C. A rare case of cotrimoxazole-induced eosinophilic aseptic meningitis in an HIV-infected patient. *Scandinavian Journal of Infectious Disease* 1998;**30**(5):530-1.

Podwall 2004

Podwall D, Gupta R, Furuya EY, Sevigny J, Resor SR. Angiostrongylus cantonensis meningitis presenting with facial nerve palsy. *Journal of Neurology* 2004;**251**(10):1280-1.

Punyagupta 1975

Punyagupta S, Juttijudata P, Bunnag T. Eosinophilic meningitis in Thailand. Clinical studies of 484 typical cases probably

caused by Angiostrongylus cantonensis. *American Journal of Tropical Medicine and Hygiene* 1975;**24**(6 Pt 1):921-31.

Quinn 1984

Quinn JP, Weinstein RA, Caplan LR. Eosinophilic meningitis and ibuprofen therapy. *Neurology* 1984;**34**(1):108-9.

Reid 1984

Reid IR, Wallis WE. The chronic and severe forms of eosinophilic meningitis. *Australian and New Zealand Journal of Medicine* 1984;**14**(2):163-5.

RevMan 2014 [Computer program]

The Nordic Cochrane Centre, The Cochrane Collaboration. Review Manager (RevMan). Version 5.3. Copenhagen: The Nordic Cochrane Centre, The Cochrane Collaboration, 2014.

Rossetti 2002

Rossetti AO, Meagher-Villemure K, Vingerhoets F, Maeder P, Bogousslavsky J. Eosinophilic aseptic arachnoiditis. A neurological complication in HIV-negative drug-addicts. *Journal of Neurology* 2002;**249**(7):884-7.

Schulz 2002

Schulz KF, Grimes DA. Allocation concealment in randomized trials: defending against deciphering. *Lancet* 2002;**359**:614-8.

Slom 2003

Slom T, Johnson S. Eosinophilic meningitis. *Current Infectious Disease Reports* 2003;**5**(4):322-8.

Tsai 2001

Tsai HC, Liu YC, Kunin CM, Lee SSJ, Chen YS, Lind HH, et al. Eosinophilic meningitis caused by Angiostrongylus cantonensis: report of 17 cases. *American Journal of Medicine* 2001;**111**(2):109-14.

Tsai 2004

Tsai HC, Lee SS, Huang CK, Yen CM, Chen ER, Liu YC. Outbreak of eosinophilic meningitis associated with drinking raw vegetable juice in southern Taiwan. *American Journal of Tropical Medicine and Hygiene* 2004;**71**(2):222-6.

Tung 1991

Tung H, Raffel C, McComb JG. Ventricular cerebrospinal fluid eosinophilia in children with ventriculoperitoneal shunts. *Journal of Neurosurgery* 1991;**75**(4):541-4.

References to other published versions of this review

Thanaviratananich 2011

Thanaviratananich S, Thanaviratananich S, Ngamjarus C. Corticosteroids with or without antihelminthics for parasitic eosinophilic meningitis. *Cochrane Database of Systematic Reviews* 2011, Issue 4. [DOI: 10.1002/14651858.CD009088]

Thanaviratananich 2012

Thanaviratananich S, Thanaviratananich S, Ngamjarus C. Corticosteroids for parasitic eosinophilic meningitis. *Cochrane Database of Systematic Reviews* 2012, Issue 10. [DOI: 10.1002/14651858.CD009088.pub2]

CHARACTERISTICS OF STUDIES

Characteristics of included studies [ordered by year of study]

Chotmongkol 2000

Methods	RCT
Participants	≥ 15 years; eosinophilic meningitis based on CSF findings
Interventions	Prednisolone 60 mg/day, 14 days
Outcomes	Number and percentage of patients who had headache after 14 days of treatment; median time until resolution of headache; number of patients who needed therapeutic lumbar puncture; and frequency of acetaminophen use
Notes	—

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	A stratified block-of-four randomisation was performed
Allocation concealment (selection bias)	High risk	Not mentioned

Chotmongkol 2000 *(Continued)*

Blinding of participants and personnel (performance bias) All outcomes	Low risk	An identical-looking placebo tablet was used as control
Blinding of outcome assessment (detection bias) All outcomes	Low risk	An identical-looking placebo tablet was used as control
Incomplete outcome data (attrition bias) All outcomes	Low risk	8/63 in the treatment group and 11/66 in the control group were lost to follow-up
Selective reporting (reporting bias)	Low risk	All important outcomes were assessed
Other bias	Unclear risk	Although the authors planned to count pills to check compliance, the compliance rate of each intervention was not described

CSF: cerebrospinal fluid
RCT: randomised controlled trial

Characteristics of excluded studies *[ordered by study ID]*

Study	Reason for exclusion
Chotmongkol 2004	Not a RCT
Chotmongkol 2006	Not a RCT
Chotmongkol 2009	No placebo group; compared prednisolone plus albendazole versus prednisolone alone
Sawanyawisuth 2004	Not a RCT

RCT: randomised controlled trial

APPENDICES

Appendix 1. MEDLINE and CENTRAL search strategy

MEDLINE (Ovid)

1 exp Meningitis/
2 meningit*.tw.
3 1 or 2
4 Eosinophilia/
5 eosinophil*.tw.
6 Parasites/
7 parasitic diseases/ or helminthiasis/ or nematode infections/
8 (parasit* or helminth* or nematod*).tw.
9 Angiostrongylus cantonensis/
10 (angiostrongylus cantonensis or "A. cantonenesis").tw.
11 ("rat lung worm" or "rat lungworm").tw.
12 (gnathostoma spinigerum or "G. spinigerum").tw.

13 (Baylisascaris procyonis or "B. procyonis").tw.
14 or/4-13
15 3 and 14
16 exp Adrenal Cortex Hormones/
17 corticosteroid*.tw,nm.
18 exp Steroids/
19 steroid*.tw,nm.
20 exp Dexamethasone/
21 (dexamethasone or dexametasone).tw,nm.
22 prednisolone.tw,nm.
23 methylprednisolone.tw,nm.
24 (betamethasone or betametasone).tw,nm.
25 triamcinolone.tw.
26 hydrocortisone.tw,nm.
27 or/16-26
28 15 and 27

Appendix 2. EMBASE.com search strategy

#1.27 #1.15 AND #1.26

#1.26 #1.16 OR #1.17 OR #1.18 OR #1.19 OR #1.20 OR #1.21 OR #1.22 OR #1.23 OR #1.24 OR #1.25

#1.25 dexamethasone:ab,ti OR dexametasone:ab,ti OR prednisolone:ab,ti OR methylprednisolone:ab,ti OR betamethasone:ab,ti OR betametasone:ab,ti OR triamcinolone:ab,ti OR hydrocortisone:ab,ti

#1.24 'dexamethasone'/de OR 'prednisolone'/de OR 'methylprednisolone'/de OR 'betamethasone'/de OR 'triamcinolone'/de OR 'hydrocortisone'/de

#1.23 'adrenal cortex hormone':ab,ti OR 'adrenal cortex hormones':ab,ti OR 'adrenal cortical hormone':ab,ti OR 'adrenal cortical hormones':ab,ti OR 'adrenal cortical steroid':ab,ti OR 'adrenal cortical steroids':ab,ti

#1.22 adrenocorticoid*:ab,ti OR corticoid*:ab,ti OR glucocorticoid*:ab,ti

#1.21 (adrenocortical NEAR/1 hormone*):ab,ti

#1.20 (adrenocortical NEAR/1 steroid*):ab,ti

#1.19 steroid*:ab,ti

#1.18 'steroid'/exp

#1.17 corticosteroid*:ab,ti

#1.16 'corticosteroid'/exp

#1.15 #1.3 AND #1.14

#1.14 #1.4 OR #1.5 OR #1.6 OR #1.7 OR #1.8 OR #1.9 OR #1.10 OR #1.11 OR #1.12 OR #1.13

#1.13 'gnathostoma spinigerum':ab,ti OR 'g. spinigerum':ab,ti OR 'baylisascaris procyonis':ab,ti OR 'b. procyonis':ab,ti

#1.12 'gnathostomiasis'/de

#1.11 'rat lungworm':ab,ti OR 'rat lung worm':ab,ti

#1.10 'angiostrongylus cantonensis':ab,ti OR 'a. cantonensis':ab,ti

#1.9 'angiostrongylus cantonensis'/de OR 'angiostrongyliasis'/de

#1.8 parasit*:ab,ti OR helminth*:ab,ti OR nematod*:ab,ti

#1.7 'parasitosis'/de OR 'helminthiasis'/de OR 'nematodiasis'/de

#1.6 'parasite'/de

#1.5 eosinophil*:ab,ti

#1.4 'eosinophilia'/de

#1.3 #1.1 OR #1.2

#1.2 meningit*:ab,ti

#1.1 'meningitis'/exp

Appendix 3. Scopus search strategy

Your query: (((TITLE-ABS-KEY(meningit*) AND TITLE-ABS-KEY(eosinophil* OR parasit* OR helminth* OR nematod* OR "angiostrongylus cantonensis" OR "A. cantonensis" OR "rat lungworm" OR "rat lung worm" OR "gnathostoma spinigerum" OR "G. spinigerum" OR "baylisascaris procyonis"))) AND ((TITLE-ABS-KEY("adrenal cortex hormones" OR corticosteroid* OR steroid* OR adrenocorticoid* OR glucocorticoid* OR "adrenocortical steroids" OR "adrenal cortex hormones" OR "adrenal cortical hormones" OR "adrenal cortical steroids") OR TITLE-ABS-KEY(dexamethasone OR dexametasone OR prednisolone OR methylprednisolone OR betamethasone OR betametasone OR triamcinolone OR hydrocortisone)))) AND ((TITLE(random* OR placebo* OR trial OR trials OR "controlled study" OR "pilot study" OR "single blind" OR "double blind" OR group OR groups) OR ABS(random* OR placebo* OR trial OR trials OR "controlled study" OR "pilot study" OR "single blind" OR "double blind" OR group OR groups)))

Appendix 4. Web of Science (ISI Thomson) search strategy

Topic=(meningit* and (eosinophil* or parasit* or helminth* or nematod* or "Angiostrongylus cantonensis" or "A. cantonensis" or "Gnathostoma spinigerum" or "G. spinigerum" or "Baylisascaris procyonis" or "B. procyonis")) AND Topic=("adrenal cortex hormones" or "adrenocortical steroids" or "adrenal cortical hormones" or "adrenal cortical steroids" or corticosteroid* or steroid* or glucosteroid* or glucocorticoid* or dexamethasone or dexametasone or prednisolone or methylprednisolone or betamethasone or betametasone or triamcinolone or hydrocortisone or adrenocorticoid* or corticoid*) Refined by: Topic=(random* or placebo* or trial or trials or "controlled study" or "pilot study" or "single blind" or "double blind" or group or groups)

Appendix 5. LILACS (Bireme) search strategy

Search > ((MH:meningitis OR meningit$ OR MH:C10.228.228.507$ OR MH:C10.228.566$) AND (MH:parasites OR parasit$OR MH:eosinophilia OR eosinophil$ OR eosinofil$ OR MH"parasitic diseases" OR "enfermedades parasitarias" OR "doenças parasitárias" OR MH:helminthiasis OR helmint$ OR MH:"nematode infections" OR "Infecciones por Nematodos" OR "Infecções por Nematóides" OR nematod$ OR Nematóides OR MH:"angiostrongylus cantonensis" OR "angiostrongylus cantonensis" or "A. cantonensis" OR "rat lungworm" OR "rat lung worm" OR "gnathostoma spinigerum" OR "G. spinigerum" OR "baylisascaris procyonis" OR "B. procyonis")) AND (MH:"adrenal cortex hormones" OR MH:D06.472.040$ OR Corticoesteroide$ OR Corticosteróide$ OR Corticoid$ OR corticosteroid$ OR MH:glucocorticoids OR glucocortic $ OR MH:steroids OR steroid$ OR Esteroide$ OR Esteróide$ OR MH:D04.808$ OR MH:dexamethsone OR dexamethason$ OR dexametason $ OR MH:prednisolone OR prednisol$ OR MH:methylprednisolone OR methylprednisolon$ OR metilprednisol$ OR MH:betamethasone OR betamethason$ OR betametason$ OR MH:triamcinolone OR triamcinolon$ OR triancinolon$ OR MH:hydrocortisone OR hydrocortison$ OR hidrocortison$)

Appendix 6. CINAHL (Ebsco) search strategy

S23 S17 and S22 6
S22 S18 or S19 or S20 or S21 34904
S21 TI (dexamethasone or dexametasone or prednisolone or methylprednisolone or betamethasone or betametasone or triamcinolone or hydrocortisone) OR AB (dexamethasone or dexametasone or prednisolone or methylprednisolone or betamethasone or betametasone or triamcinolone or hydrocortisone) 2727
S20 TI (corticosteroid* or steroid* or adrenocorticoid* or corticoid* or glucocorticoid* or adrenocortical hormone* or adrenocortical steroid* or adrenal cortex hormone* or adrenal cortical hormone* or adrenal cortical steroid*) OR AB (corticosteroid* or steroid* or adrenocorticoid* or corticoid* or glucocorticoid* or adrenocortical hormone* or adrenocortical steroid* or adrenal cortex hormone* or adrenal cortical hormone* or adrenal cortical steroid*) 1875
S19 (MH "Steroids+") 22513
S18 (MH "Adrenal Cortex Hormones+") 10803
S17 S3 and S16 33
S16 S4 or S5 or S6 or S7 or S8 or S9 or S10 or S11 or S12 or S13 or S14 or S15 4202
S15 TI ("rat lungworm" or "rat lung worm") OR AB ("rat lungworm" or "rat lung worm") 2
S14 TI ("Baylisascaris procyonis" or "B. procyonis") OR AB ("Baylisascaris procyonis" or "B. procyonis") 2

S13 TI ("gnathostoma spinigerum" or "G. spinigerum") OR AB ("gnathostoma spinigerum" or "G. spinigerum") 0
S12 TI ("angiostrongylus cantonensis" or "A. cantonensis") OR AB ("angiostrongylus cantonensis" or "A. cantonensis") 6
S11 TI (parasit* or helminth* or nematod*) OR AB (parasit* or helminth* or nematod*) 1724
S10 (MH "Nematode Infections") OR (MH "Helminthiasis") 410
S9 (MH "Helminths") OR (MH "Nematodes") 308
S8 (MH "Parasitic Diseases") OR (MH "Central Nervous System Helminthiasis") OR (MH "Central Nervous System Parasitic Infections") 605
S7 TI parasit* OR AB parasit* 1567
S6 (MH "Parasites") 169
S5 TI eosinophil* OR AB eosinophil* 1515
S4 (MH "Eosinophilia") 591
S3 S1 or S2 3268
S2 TI meningit* OR AB meningit* 2235
S1 (MH "Meningitis+") 2546

WHAT'S NEW

Date	Event	Description
10 December 2014	New search has been performed	Searches updated. We did not identify any new trials for inclusion or exclusion.
10 December 2014	New citation required but conclusions have not changed	Our conclusions remain unchanged.

CONTRIBUTIONS OF AUTHORS

Sikawat Thanaviratananich (SiT) developed the protocol, searched the literature, selected studies, extracted data, assessed the quality of included trials and wrote the review.
Sanguansak Thanaviratananich (SaT) helped to develop the protocol, selected studies, extracted data, assessed the quality of included trials and edited the review.
Chetta Ngamjarus (CN) helped to edit the protocol, performed data analysis and edited the review.

DECLARATIONS OF INTEREST

Sikawat Thanaviratananich: none known.
Sanguansak Thanaviratananich: none known.
Chetta Ngamjarus: none known.

SOURCES OF SUPPORT

Internal sources

- Department of General Medicine, Khon Kaen Hospital, Thailand.
- Department of Otorhinolaryngology, Faculty of Medicine, Khon Kaen University, Thailand.
- Department of Biostatistics and Demography, Faculty of Public Health, Khon Kaen University, Thailand.

External sources

- Thai Cochrane Network, Thailand.

DIFFERENCES BETWEEN PROTOCOL AND REVIEW

We changed some outcomes to be consistent with the outcomes in most of the studies we identified. These included changing from resolution rate of headache to the number of patients who still had headaches after 14 days of treatment and changing the percentage of analgesics used to relieve symptoms to the median time of analgesic use.

INDEX TERMS

Medical Subject Headings (MeSH)

Central Nervous System Parasitic Infections [*drug therapy]; Eosinophilia [*drug therapy]; Glucocorticoids [*therapeutic use]; Meningitis [*drug therapy]; Prednisolone [*therapeutic use]; Randomized Controlled Trials as Topic

MeSH check words

Animals; Humans